

Commentary

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Is atherosclerosis caused by high cholesterol?

U. RAVNSKOV

Introduction

According to the low-density-lipoprotein (LDL) receptor hypothesis, development of atherosclerosis is caused by a high concentration of LDL-cholesterol in the blood, and lowering LDL-cholesterol reverses, or at least retards, atherosclerosis, thus preventing cardiovascular disease.¹ As a scientific hypothesis, it is open to falsification: if the concentration of LDL-cholesterol or total cholesterol and the degree of atherosclerosis do not correlate, or if there is no exposure-response, e.g. if there is no association between the cholesterol changes (Δ LDL-cholesterol or Δ total cholesterol) and atherosclerosis progression.

The successful statin trials, with their substantial reduction of LDL-cholesterol seemed to confirm the LDL receptor hypothesis, but their outcome was independent of the initial cholesterol concentration and the degree of its lowering. For instance, the *p* values for the relationships between the outcome, and the percentage or the absolute change in LDL cholesterol, as calculated in one of the trial reports,² were 0.76 and 0.97, respectively. The lack of exposure-response, together with the benefit of the treatment in disorders and age groups where LDL-cholesterol concentration has little if any predictive value, suggests that statins must have more important effects on cardiovascular disease than a lowering of cholesterol.³ Indeed, there is evidence that the statins have anti-thrombotic and anti-inflammatory effects, and also a beneficial influence on endothelial dysfunction, LDL oxidation, re-vascularization and smooth muscle cell proliferation.

Even if these effects were operating in the trials, the substantial lowering of LDL-cholesterol

should at least have contributed to the improvement if the LDL receptor hypothesis were correct. The lack of exposure-response also questions whether atherosclerosis is truly caused by high LDL-cholesterol.

However, the outcome in the clinical trials was cardiovascular disease, not atherosclerotic progression. To answer the question, we need to compare the cholesterol concentration and the degree of atherosclerosis, and in particular, to study the influence of Δ LDL-cholesterol on atherosclerotic progression, rather than clinical outcome.

Cholesterol does not predict degree of atherosclerosis at autopsy

In 1936, Landé and Sperry noted that the degree of aortic atherosclerosis at autopsy of healthy individuals who had died violently, was independent on their blood cholesterol concentration analysed immediately after death.⁴ Their finding was confirmed by Mathur *et al.*⁵ and similar results were obtained by others.^{6–8} The objection that an analysis of cholesterol after death may not reflect its concentration during life was met by Mathur *et al.*⁵ who found that the cholesterol concentration was almost constant up to 16 h after death. Paterson *et al.*⁶ bypassed the problem by comparing the degree of atherosclerosis at death with the individuals' cholesterol measured previously on several occasions. In all these studies, plots of blood cholesterol concentrations vs. the lipid content of the aorta or the coronary arteries were widely scattered.

Address correspondence to Dr U. Ravnskov, Magle Stora Kyrkogata 9, S-22350 Lund, Sweden. e-mail: uffe.ravnskov@swipnet.se

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More recent autopsy studies have found weak or inconsistent correlations between LDL-cholesterol or total cholesterol and various measures of atherosclerosis.⁹ For instance, the most severe degree of atherosclerosis was found mainly in individuals with extremely high cholesterol, whereas small differences were seen in the rest.¹⁰ A correlation was found in White men, but not in Black men,¹¹ in men but not in women,¹² in individuals below, but not above age 80 years,¹³ and in the coronary arteries, but not in the thoracic or abdominal aorta.¹⁴

The weak and unpredictable correlations probably reflect bias, because most of the studies were performed on selected individuals. In such large projects, the main object of which was to study risk factors for cardiovascular disease, individuals with such diseases, or with high cholesterol, were preferred for post-mortem examination,^{10–15} which means that the proportion of individuals with familial hypercholesterolaemia must have been much larger than in the general population. As such patients have very high cholesterol and are more prone to vascular changes, their inclusion automatically creates a correlation between degree of atherosclerosis and LDL or total cholesterol. Accordingly, it is obvious from a figure in a preliminary report that the correlation disappears if individuals with total cholesterol >350 mg/ml (9 mmol/l) are excluded.¹⁶ It is questionable if the vascular changes seen in familial hypercholesterolaemia are synonymous with atherosclerosis.^{17,18} Therefore, to prove that the concentration of LDL-cholesterol has importance in the general population, it is necessary to exclude individuals with familial hypercholesterolaemia.

Cholesterol does not correlate with degree of coronary atherosclerosis on angiography

A correlation between the pathological findings seen on coronary angiography and cholesterol has been found in many studies.¹⁹ However, the correlation coefficients in these studies were never >0.36 and often much smaller; in some studies no correlation was found.^{20–23} When present, the correlation found may have been due to bias by the process mentioned above, because coronary angiography is mainly performed on patients with symptomatic coronary disease, and more often on middle-aged and younger patients. The correlation disappeared in one study after exclusion of patients treated with lipid-lowering drugs.²⁴

Cholesterol does not correlate with degree of coronary calcification

In contrast to conventional angiography, electron beam angiography detects coronary plaques independent of their location in the vessel wall, but only calcified plaques. Degree of coronary calcification seems a good surrogate for degree of coronary atherosclerosis, because it correlates strongly with total plaque volume and obstructive coronary disease, and is a powerful predictor of clinical outcome. Nonetheless, degree of coronary calcification did not correlate with any lipid fraction in the blood.²⁵

Cholesterol does not correlate with degree of peripheral atherosclerosis

Many studies have found an association between LDL- or total cholesterol and peripheral atherosclerosis, depicted by angiography or ultrasonography, but only in dichotomous analyses, and again, differences have been found mainly between individuals with very high cholesterol concentrations and the rest. In ultrasonographic studies, where degree of carotid atherosclerosis was graded as a continuous variable, no correlation was found with individual LDL-cholesterol concentrations.^{26,27} In similar studies using aortic²⁸ and femoral²⁹ angiography, no correlation was found either. Mean femoral intima-media thickness was evaluated by ultrasonography in patients with familial hypercholesterolaemia and in control individuals with normal cholesterol. Using all observations, a correlation was found ($r=0.41$), but from a visual judgement of the scatterplot, within each group no clear correlation was present.³⁰

No exposure-response

The lack of an association in these studies may be explained by an influence of other important risk factors. A more reliable parameter is exposure-response. If the amount of circulating cholesterol has any importance, sequential changes of its concentrations should be followed by parallel changes of atherosclerosis growth.

In a few observational studies with coronary angiography, the correlation of these two parameters, graded as continuous variables, was analysed. In three studies, no correlation was found;^{32–34} in two others, progression of atherosclerosis was associated with a decrease in cholesterol, not an increase.^{35,36}

Experimentally, many trials have analysed the effect of cholesterol lowering on the angiographic changes. Most of them have looked at the association with on-trial LDL-cholesterol or final LDL-cholesterol only, but in sixteen trials,^{36–51} exposure-response was also analysed (Table 1). Two of them found exposure-response. In one of them Δ LDL-cholesterol and Δ total cholesterol were larger in the non-progression group, but only in a unifactorial analysis.⁴³ In another trial, treadmill exercise was used as intervention only. After one year, degree of exercise and Δ LDL-cholesterol, but not Δ total cholesterol, were inversely associated with the rate of progression.⁴⁰ In the rest of the trials exposure-response was absent (Table 1).

Several explanations were offered: most commonly that other lipids or lipid combinations explained the findings. However, Δ high-density lipoprotein (HDL) cholesterol was analysed in twelve studies,^{36–38,40–44,46,47,50,51} Δ triglycerides in ten,^{36–38,40–42,44,47,50,51} Δ apo-lipoprotein B in six,^{37,42,47,48,50,51} Δ apo-lipoprotein A1 in three,^{37,47} Δ very-low-density-lipoprotein cholesterol in three,^{36,50,51} and Δ small, dense LDL-cholesterol in one study,⁵⁰ but none of them were associated with atherosclerosis growth. In an early trial using visual evaluation of the angiographic findings³⁶ Δ intermediate-density lipoprotein cholesterol was associated with atherosclerotic progression, but in two others using computer-assisted analysis,^{50,51} no association was found. In three trials, the ratio Δ total cholesterol/HDL cholesterol was inversely associated with atherosclerotic progression,^{41,43,47} but in one it was seen only in the placebo group,⁴¹ and in another the analysis was not corrected for other risk factors.⁴³

Objections

Doubt has been raised against the use of coronary angiography as a measure of atherosclerotic changes.⁵² The most serious objection, that angiography underestimates the amount of subendothelial deposits, and cannot depict the intramural ones, is not relevant in studies of exposure-response, because associations are sought to the changes, not to the degree of atherosclerosis. Large inter- and intra-observer variabilities are found in studies using visual judgement of the angiographic changes, but thirteen of the sixteen mentioned trials used quantitative, computerized image analysis (Table 1). Other objections include imprecise measurements of lumen diameter and misinterpretation of its initial compensatory enlargement as atherosclerotic regression. In particular, percent stenosis has been questioned as a reliable measure

of progress or regress because of uncontrolled physiological influences on the lumen of the reference vessels.^{52–54} However, if measured with care, the minimum lumen diameter, used in half of the studies as a measure of atherosclerosis (Table 1), has a low coefficient of variation for repeated measurements⁵⁵ and is a strong predictor of the coronary flow reserve,⁵⁶ the reactive hyperaemic response,⁵³ the transstenotic pressure gradient⁵⁷ and thallium scintigraphic changes after exercise,⁵⁷ all of which reflect degree of atherosclerotic narrowing of the coronary vessels. Angiographic deterioration strongly predicted cardiovascular events in the studies that included a clinical follow-up.^{36,37,39}

Why does a high cholesterol predict cardiovascular disease?

If LDL-cholesterol and Δ LDL-cholesterol do not correlate with degree of atherosclerosis or with atherosclerosis growth, why does a high cholesterol predict cardiovascular disease? The answer may be that cardiovascular disease is not synonymous with atherosclerosis. A high LDL or total cholesterol may be secondary to uncontrolled factors that promote cardiovascular disease in other ways and cause hypercholesterolaemia at the same time, for instance lack of physical activity,⁵⁸ mental stress,⁵⁹ smoking, and obesity.⁶⁰ It is generally assumed that their effect on cardiovascular disease is mediated through the high cholesterol, but this may be a secondary phenomenon. Physical activity may benefit the cardiovascular system by improving endothelial function,⁶¹ or by stimulating the formation of collateral vessels,⁶² mental stress may have a harmful influence on adrenal hormone secretion, smoking increases the oxidant burden; in these all situations the high cholesterol may be an epiphenomenal indicator that something is wrong. This argument also explains why some studies found atherosclerotic growth to be associated with initial or on-study LDL-cholesterol, but not with Δ LDL or total cholesterol. If the amount of LDL-cholesterol in the blood were the determining factor, atherosclerotic growth should have been associated with Δ LDL-cholesterol as well and to a higher degree.

Conclusion

'The more LDL there is in the blood, the more rapidly atherosclerosis develops.' This 1984 statement by the Nobel Award winners Michael Brown and Joseph Goldstein¹ has dominated research

Table 1 Changes (Δ) in low-density lipoprotein cholesterol and of total cholesterol in relation to atherosclerotic progression, graded as a continuous variable, in 18 cholesterol-lowering, angiographic trials

Trial	Type of intervention	Measurement of angiographic progress or regress	Baseline LDL-C and (tC) (mmol/l)	Trial length (years, months)	Patients		Increase in atherosclerosis associated with	
					n	Males (%)		Mean age (years)
							Δ tC	Δ LDL-C
Krauss <i>et al.</i> 1987 ³⁶	Cholestyramine	MLD c, v	6.08 (7.08)	5,0	143	80	No*	No*
Blankenhorn <i>et al.</i> 1990 ³⁷	Colestipol, niacin	MLD c, v	4.36 (6.26)	2,0	162	100	No*	No*
Olsson <i>et al.</i> 1990 ³⁸	Nicotinic acid + fenofibrate	Global estimate f, v	6.44 (9.68)	1,6	20	100	No	No
Tatami <i>et al.</i> 1992 ³⁹	LDL-apheresis + probucol and/or pravastatin	%Stenosis c, q	8.89 (11.1)	>1,0	37	59	No*	No*
Hambrecht <i>et al.</i> 1993 ⁴⁰	Physical exercise	MLD; %stenosis c, q	4.21 (6.0)	1,0	88	100	No*	Yes*
Hodis <i>et al.</i> 1994 ⁴¹	Lovastatin	%Stenosis c, q	4.00 (5.90)	2,0	220	91	No*	No*
Sacks <i>et al.</i> 1994 ⁴²	Various lipid-lowering drugs	MLD; %stenosis c, q	3.56 (5.5)	2,9	79	89	No*	No*
Quinn <i>et al.</i> 1994 ⁴³	Multiple risk factor reduction	MLD c, q	4.02 (5.88)	2,0	257	86	Yes	Yes
Schuff-Werner <i>et al.</i> 1994 ⁴⁴	LDL-apheresis	%Stenosis c, q	7.54 (9.36)	2,0	33	70	No	No
Kitabatake <i>et al.</i> 1994 ⁴⁵	LDL-apheresis + various lipid-lowering drugs	%Stenosis, c, q	6.62 (8.46)	1,0	13	77	-	No
Regnström <i>et al.</i> 1996 ⁴⁶	Probucol	Global estimate f, q	6.52 (8.83)	3,0	303	57	No	No
Niebauer <i>et al.</i> 1996 ⁴⁷	Low-fat diet + physical exercise	%Stenosis c, q	4.22 (6.06)	1,0	92	100	No*	No*
Kroon <i>et al.</i> 1996 ⁴⁸	LDL-apheresis + simvastatin vs. simvastatin	MLD; %stenosis c, q	7.82 (9.79)	2,0	40	100	No	No
Tamura <i>et al.</i> 1997 ⁴⁹	Pravastatin	%Stenosis c, q	3.11 (4.73)	2,0	80	81	No	No
Ruotolo <i>et al.</i> 1998 ⁵⁰	Bezafibrate	MLD; %stenosis c, q	4.64	5,0	81	100	-	No*
Sutherland <i>et al.</i> 1998 ⁵¹	Simvastatin	% stenosis c, q	4.33 (6.91)	2,0	38	53	No	No

*Adjusted for other risk factors; MLD, minimum lumen diameter; LDL-C, LDL-cholesterol; tC, total cholesterol; c, coronary angiography; f, femoral angiography; v, visual judgement; q, quantitative, computerized image analysis.

on atherosclerosis since then. As shown here, this hypothesis appears to be falsified by the fact that degree of atherosclerosis, and atherosclerotic growth, were independent on the concentration or the change of LDL-cholesterol in almost all studies. The role of LDL-cholesterol for atherosclerosis growth has been exaggerated, a finding with consequences for the prevention of cardiovascular disease. For instance, as the statins exert their beneficial influence on the cardiovascular system by several mechanisms, it may be wiser to search for the lowest effective dose instead of the dose with maximal effect on LDL-cholesterol. Neither should an elevated LDL-cholesterol be the primary target in cardiovascular prevention, as recently claimed by the American National Cholesterol Education Program, and researchers should direct more attention to other hypotheses.

I may have overlooked studies that have found an association between changes of LDL-cholesterol or other lipid fractions, and atherosclerotic progression. However, although the presence of exposure-response is not sufficient proof in itself of causality, it is difficult to explain its absence.

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